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Award Number: W81XWH-05-1-0093

TITLE: Long-Term Outcomes of Alternative Brachytherapy Techniques for Early Prostate Cancer

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REPORT DATE: January 2008

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-01-2008	Final	30 DEC 2004 - 29 DEC 2007

4. TITLE AND SUBTITLE

Long-Term Outcomes of Alternative Brachytherapy Techniques for Early Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-05-1-0093

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
James A. Talcott, M.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Massachusetts General Hospital
Boston, Massachusetts 02114

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

All active, potentially curative treatments for clinically localized prostate cancer damage quality of life. Brachytherapy, or radioactive seed implants, theoretically may increase the target radiation dose and thus improve control of cancer. It has been rapidly adopted in the U.S. despite limited long-term published outcomes, in part because of its convenience and apparently attractive toxicity profile. However, our recent survey of brachytherapy patients after longer follow-up found surprisingly frequent urinary incontinence and erectile dysfunction. Retrospective evidence suggests that reducing the radiation dose to the urethra may prevent later urinary incontinence. A recent refinement of conventional brachytherapy technique targets only the peripheral zone of the prostate, sharply reducing the dose to the urethra, and attempts to reduce radiation "cold spots" by using intraoperative feedback from real-time magnetic resonance imaging (MRI). Using our validated cancer-specific scales, our pilot data suggested that the altered brachytherapy technique had the intended benefit but also unexpected outcomes. We have extended our cohort study of 276 brachytherapy patients and now compare 3- and 24-month outcomes of this technique to standard ultrasounded-guided brachytherapy.

15. SUBJECT TERMS
Quality of Life, Outcomes, bowel symptoms, sexual function, questionnaires, magnetic resonance imaging

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
U	U	U	UU	17	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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BACKGROUND

Prostate cancer is a unique malignancy because of the uncertain but probably modest efficacy of available local treatments for early (non-metastatic) cancer, the potential for long-lasting treatment-related urinary, bowel and sexual function problems, its unusually long typical natural history. As a result the great majority of patients experience any permanent symptoms for more than a decade, and its great impact on the American population, the highest incidence and second highest prevalence of any non-cutaneous malignancy in the United States (1). The most recent estimate is over 1.8 million men. Nearly one million had survived 5 years and a quarter million 10 years or more. Most men are diagnosed with early (non-metastatic) cancer, for which local therapy may be curative, but because of the prostate's anatomical location may lead to sexual, urinary and bowel dysfunction (2-6). The great majority of these men will be treated with either external beam radiation therapy (XRT), radical prostatectomy (RP), or ultrasound guided interstitial prostate radiation therapy (BT), also known as brachytherapy or seed implants. BT is now widely available, despite still sparse efficacy data (7, 8). Complication rates of the alternative local treatments differ qualitatively and quantitatively. All active treatments for prostate cancer produce erectile dysfunction (ED) in most men, and long-term urinary incontinence (after RP and brachytherapy) and bowel dysfunction (after EBRT) are common (3, 5, 6, 9-14).

Although early experience with brachytherapy using freehand placement of radioactive seeds in open pelvic surgery yielded both unsatisfactory control of cancer and high post-treatment complication rates (15-18), a percutaneous ultrasound-guided technique developed by Blasko, Ragde and colleagues in Seattle dramatically improved three-dimensional radiation dose distributions (13-15). As a result, brachytherapy was reevaluated (7), resulting in its now wide availability in the United States (19). Randomized comparisons between modalities are rare and flawed, although a randomized trial of RP vs. initial observation has recently found evidence of a small benefit for surgery (20, 21) at a cost in quality of life (22). Retrospective, prognostically-stratified comparisons of RP to XRT have appeared (23, 24), and more recently one between ultrasound-guided brachytherapy and RP or XRT (8). Based on a multivariable time to PSA failure analysis of patients stratified by previously-defined pretreatment risk groups, low risk patients ($T_{1c, 2a}$ and PSA $\leq$ 10 and Gleason $\leq$ 6) had comparable PSA failure free survival at 5 years after RP, XRT, or brachytherapy, but brachytherapy patients at high (T_{2c} or PSA > 20 or Gleason $\geq$ 8) or intermediate risk (T_{2b} or Gleason 7 or PSA > 10 and $\leq$ 20) had significantly worse cancer control than patients managed with RP or XRT.

BT, like other prostate cancer treatments, affects patient quality of life. Our team documented one of the most important complications, the risk of long-term urinary incontinence. Although acute urethral irritation and urinary obstruction are well-documented short-term complications of standard ultrasound-guided BT (27-33), reports by treating physicians after relatively short follow-up (median 18-45 months) indicates little evidence of long-term complications (27-29, 31, 34). However, because of the potentially long delay after brachytherapy for some symptoms, especially urinary incontinence and erectile dysfunction (ED), and the usually greater complication rates obtained directly from patients rather than treating physicians, in part because of patients' reluctance to complain to their doctors (2, 5, 6, 11, 35), we felt these reports may underreport long-term complications of BT, especially urinary incontinence and erectile dysfunction. However, there is some evidence that the bowel problems associated with external beam radiation therapy (EBRT) are less frequent in BT.

To better define long-term BT-associated side effects, we performed a cross sectional survey of the earliest large patient cohort treated by the Seattle group completed at a median of 5 years after treatment. We found that 38% of BT patients who had not had comorbid procedures like transurethral resection of the prostate (TURP) reported some degree of urinary incontinence. These results may be partly explained by the older age of the patients in that early cohort (median: 75 years) and by preexisting pretreatment dysfunction our cross-sectional survey could not document. However, the outcome is consistent with the phenomenon of acute urethral necrosis the Seattle physician group had previously described (36), and the prevalence of urinary incontinence we found is much higher than expected in men in that age group. Subsequent retrospective studies supported the belief that the primary risk factor producing long-term incontinence is the proportion of the urethra receiving high-dose radiation (31, 37). Reduced radiation to the urethra was subsequently associated with reduced incontinence (38). The MBT technique addresses this problem by excluding the periurethral transition zone of the prostate from the target volume for radiation, trading the risk of allowing cancer in the transition zone to persist after treatment in exchange for decreased urethral irradiation in the hope that late urinary incontinence will also be decreased. Because cancers in the transition zone are much less frequent than those in the peripheral zone and may have a more indolent course, this technical change may benefit patients overall, although the benefit and harms require empirical verification. This project follows on a recently completed project, Outcomes of Alternative Brachytherapy Techniques for Early Prostate Cancer (DAMD17-02-1-0090), to determine whether a quality of life benefit can be demonstrated in the first 2 years after BT. The current project continues that project for an additional 3 years. Unfortunately, the first project was delayed by 10 months for DAMD IRB review of the project, which had previously been approved by all participating institutions' own IRBs. Therefore, follow-up is delayed by that amount. We present interim results from the new study, which closely overlap the results we presented in the Final Report of the earlier project.

METHODS

Patient Population

Patients are recruited from 4 Boston-area treatment programs directed by three outstanding brachytherapy experts: Brigham and Women's Hospital, directed by Dr. Anthony D'Amico, the Massachusetts General Hospital, directed by Dr. Anthony Zietman, and Beth Israel –Deaconess and MetroWest Hospitals, both directed by Dr. Irving Kaplan. The first 3 sites are in Boston and the fourth in Framingham, MA. Before treatment, investigators or study staff at the Massachusetts General Hospital Center for Outcomes Research give or send all eligible patients the baseline study instrument, along with a cover letter describing the study from the Principal Investigator and their treating physician. The few patients who do not respond within two weeks are contacted by telephone. Enrolled patients are registered with the Quality Assurance Office for Clinical Trials (QAOCT) at the Dana Farber Cancer Institute by study staff.

At each specified follow-up interval from initiation of therapy, 3, 12, 24, 36, 48 and 60 months, we mail patients a cover letter and follow-up questionnaires containing the same instruments as the pretreatment baseline questionnaire, along with postage paid return envelopes. Data are collected by the staff of the Center for Outcomes Research at Massachusetts General Hospital. Using an in-house relational database system, study participants are assigned a unique study identification number used to track the patients until follow-up is complete or the patient

drops out of the study. Automated follow-up procedures flag when participants should receive a postcard, follow-up mailing, or telephone call. Weekly statistical reports detail the status of respondents. Data management is performed at QAOCT, the data management center for all studies of the Dana Farber/Partners Cancer Care. The QAOCT data manager confirm eligibility, register patients and ensure that study parameters are followed.

Data Collection

Patients are asked to complete self-administered questionnaires that include assessments of sexual function, urinary and bowel complications of treatment, and disease-focused quality of life we previously validated (39, 40). An experienced genitourinary oncology research nurse abstracts information from medical records regarding demographic characteristics, cancer prognostic factors, comorbid diseases, treatments and subsequent clinical course using the forms developed in earlier studies.

1. Urinary, Sexual and Bowel Function. Patient-completed questionnaires included four symptom indices to assess urinary incontinence, urinary obstruction/irritation, bowel dysfunction, and sexual dysfunction. We reported previously the clinical derivation of these indices and psychometric evaluation of their reliability, validity, and responsiveness to treatment effects.(references) The Urinary Incontinence Index contains 3 questions gauging the degree of urinary control. The Urinary Obstruction and Irritation Index contains 5 questions assessing hesitancy, frequency, nocturia, dysuria, and urgency. Sexual function was measured by a core set of validated items and scales that assess patients' perceptions of their erectile function, and the quality of orgasm and ejaculation. This core set of items will be augmented by items that assess interest in sexual activity (i.e., libido), frequency of sexual activity, and satisfaction with sexual activity. In addition, we administered the five-item sexual function/quality of life scale developed in the Medical Outcomes Study (reference), also used in our previous studies. The internal consistency of this scale in early prostate cancer patients is very high (α =.90). Bowel Problems items include diarrhea, urgency of bowel movements, rectal pain, bleeding, passing mucus, abdominal cramping, and tenesmus.

Each index was scored by summing the component items and then standardizing that value to vary from 0 (no dysfunction) to 100 (maximum dysfunction).

RESULTS

As of February 2008, the project has recruited a total of 296 patients, including 215 in the two ultrasound-guided "conventional" brachytherapy treatment groups ($USBT_1$ and $USBT_2$) and 81 in the MRI-guided treatment group (MBT). Each patient completed the baseline questionnaire (See Appendix, Baseline Questionnaire) before treatment. Follow-up questionnaires have been received as follows: 246 1-Month Questionnaires (85% of the 288 enrolled and eligible patients now at least 1 month after treatment, including 16 patients who dropped out of the study before the first follow-up questionnaire), 256 3-Month Questionnaires (89% of 288 patients 3 months out, with 25 total dropouts), 241 12-Month Questionnaires (86% of 280 patients 12 months out, with 28 total dropouts), 216 24-Month Questionnaires (82% of 264 patients 24 months out, with 28 total dropouts), 168 36-Month Questionnaires (75% of 225 patients 36 months out, with 36 total dropouts), 90 48-Month Questionnaires (57% of 159 patients 48 months out, with 36 total dropouts), and 23 60-Month Questionnaires (29% of 79 patients 60 months out, with 36 total dropouts). The retention in the study has been very good, with only 20 patients dropping out after 3-month follow-up, although additional 40 patients have not yet returned their most recent

questionnaire, of whom 31 received them more than 1 month ago and may drop out of the study. We report the results of the most recent analysis, as of April 15, 2008.

Pretreatment characteristics. The enrolled patients include 81 patients who received the experimental MRI-guided technique (MRBT) and 215 patients receiving conventional ultrasound-guided brachytherapy (SBT), 115 patients treated by one physician ($USBT_1$) and 100 patients treated by another ($USBT_2$) (Table 1). The entire group was predominantly Caucasian and socioeconomically advantaged. More than three-fourths were currently married at study enrollment and had attended at least some college, and nearly 30% in both treatment groups had graduate degrees. Patients enrolled in the study were close to the median age at diagnosis for prostate cancer patients, currently 68 years, and older than many current surgical cohorts, especially those reported from referral centers, which attract patients younger, healthier and more mobile compared to those treated in community facilities. However, the MRBT group was both younger and better educated compared to the USBT group, and the $USBT_1$ patients were older than the $USBT_1$ group.

Functional Outcomes. Because of occasional omitted responses and incomplete, ongoing data entry, baseline scores for treatment-related dysfunction could be calculated for at most 245 of the 296 enrolled patients. Study patients had little reported urinary incontinence or bowel problems before treatment, with all mean baseline dysfunction scores less than 5 (Table 2). However, urinary obstruction/irritation was evident, and patients reported even more sexual dysfunction, with less pretreatment dysfunction for the MRBT group in both categories. Further, the MRBT patient group had less increase in both urinary obstruction/irritation and incontinence between baseline and 3 months ($P = 0.0000$ and 0.035, respectively). These benefits continued to be statistically significant or nearly so through 24 months, but progressively smaller sample sizes and resolution of acute symptoms resulted in lesser differences that did not achieve statistical significance thereafter in data so far (Tables 2-7).

However, our study documented increased dysfunction for all scales after treatment. We omit the 1-month results. Although we surveyed patients 1 month after treatment to ensure that symptoms did not decline between 1 and 3 months after treatment, the 1-month scores differed little from the 3-month scores.

Urinary and bowel dysfunction were greatest for all groups at 3 months after treatment, while sexual dysfunction increased steadily through 48 months, consistent with our prior observations and those of others. However, we also found differences in the outcomes between groups receiving different brachytherapy techniques. Surprisingly, we found differences not only between the MBT and USBT groups, but also between the USBT treatment groups.

CONCLUSIONS

Our study, as yet immature, adds substantial new information to the question of whether modifying brachytherapy technique can result in improved functional outcomes by reducing treatment-related toxicity. Despite incomplete follow-up, our results provide gratifying confirmatory evidence that the MBT technique, which sharply reduces radiation to the periurethral transition zone of the prostate, produces the intended reduction in short-term urinary symptoms of a probably clinically significant magnitude, at least for some patients, measured by both urinary incontinence and urinary obstruction/irritation scales. These results are consistent with our earlier observation, made in a less satisfactory study population (42). While reassuring

and indicating potential relief from the threat of worsened short-term symptoms of urinary obstruction/irritation and presumably decreased risk of potentially very painful complete urinary obstruction, these results do not directly address what many consider the most serious urinary problem caused by brachytherapy, the risk of long-term urinary incontinence, the presumed consequence of acute urethral necrosis, described by Blasko and colleagues in the pioneering Seattle brachytherapy group (27). We have argued elsewhere that since the magnitude or these urinary symptoms is primarily determined by the same cause, the intensity and extent of urethral radiation, it is reasonable to consider short-term urinary symptoms, especially when parallel results parallel results are found using 2 distinct, validated measures of urinary function (42). However we have found no evidence yet of the onset of late incontinence in any group in our current analyses. Continued follow-up will be essential to fully test for late urinary incontinence.

Other results are less consistent with our earlier report. We found little evidence that MBT patients experience greater treatment-induced bowel problems compared to USBT patients nor that they experience less sexual dysfunction, as we had reported earlier (42). The latter result was disconcerting, because of the better pretreatment sexual function of the MBT patient group, a possible indicator or lesser vulnerability to treatment-induced dysfunction but also leaving a greater potential for functional loss. However, the potential for confounding implied in noting the better MBT patients' baseline sexual function suggests an alternate explanation for the earlier observation. While the MBT patient group at baseline gave evidence of self-selection that might lead to better functional outcomes, those differences were much greater in the earlier study population (42). Therefore, the earlier observation may have simply reflected confounding by treatment indication, as we noted in the earlier report.

Finally, however, to our surprise, we found differences of comparable magnitude *between* USBT subgroups in the mean increases in both urinary dysfunction scales, suggesting that factors other than the MBT technique's planned reduction in periurethral radiation can produce substantial differences in short-term treatment-related urinary symptoms, as well as in the bowel problems and sexual dysfunction scales. This entirely unexpected result is on one hand unsurprising, since it implies that a medical technology differs in its results depending on the treatment team and other unspecified factors. Given the complexity of prostate brachytherapy, such variability should be even more expected. The variability in functional outcomes between USBT groups obscured differences between MBT and USBT by increasing variability in the outcome measures. However, it provides an additional line of investigation, which we plan to pursue, examining factors that may be associated with variations in patients outcomes within USBT patient subgroups.

Summary. Our initial comparison of functional outcomes provides support for both our earlier observations and the guiding assumption that motivated the development of the MBT technique, the belief that avoiding urethral irradiation can importantly ablate acute treatment-related urinary symptoms, and provides hope that such changes can attenuate long-term urinary incontinence, due to acute urethral necrosis, a likely related and perhaps more serious treatment-related quality of life problem. We found less support for our earlier observations that MBT increases treatment-related bowel dysfunction or decreases treatment-related sexual dysfunction, although these results suggest that confounding may have accounted for the earlier observations, as we suggested. Finally, the substantial differences in outcomes between USBT subgroups raise the possibility of identifying important additional factors that may increase of attenuate the treatment-related complications of brachytherapy.

Abbreviations

CT	computed tomography
CTV	clinical target volume
DVH	dose volume histogram
MR	magnetic resonance
MRI	magnetic resonance imaging
MBT	magnetic resonance image guided prostate brachytherapy
MRI	magnetic resonance imaging
PSA	prostate-specific antigen
XRT	radiation therapy
PR	radical prostatectomy

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TABLES

Table 1. Sociodemographic and clinical characteristics of 286 patients with early prostate cancer who underwent brachytherapy and completed baseline forms

Characteristic	Level	MRI-guided BT	All U/S-guided BT	U/S-guided BT (1)	U/S-guided BT (2)	P-value†
Number of patients		81	215	115	100	
Age	Mean	64.6	67.3	68.4	66.1	0.003
	Range	48.8-80.0	47.0-81.7	47.0-81.7	48.1-79.3	0.02
Race	Caucasian	76 (95)	201 (95%)	104(94)	97 (97)	0.62
	African-American	4 (5	8 (4%)	6 (5)	2 (2)	0.43
	Asian	0 (0%)	2 (1%)	1 (1)	1 (1%)	
	Unknown (n)	1	4	4	0	
Currently married	No (%)	61 (76)	164 (77%)	85 (75)	79 (79)	0.71
	Unknown (n)	5	1	1	0	0.36
Highest education, number (%)	Completed high school or less	7 (9)	49 (23)	26 (23)	23 (24)	<0.000
	Attended college	31 (39)	102 (49)	55 (49)	47 (48)	0.99
	Graduate/professional degree	41 (52)	59 (28)	32 (28)	27 (28)	
	Unknown (n)	2	5	2	3	

†MRI-guided vs. ultrasound (U/S)-guided brachytherapy (BT). P-values in red are for U/S-guided BT (1) vs U/S-guided BT (2.)

Table 2. Mean treatment-related function scores at baseline, at 3 months after treatment and changes for patients who completed responses.

	Patients Responding	Baseline Score	(SD)	3 Months Score	(SD)	Baseline to 3 mo. Change Score	(SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	158	17.8	(11.1)	41.3	(20.0)	23.6	20.3	0.0000
Hospital 1	86	17.4	(10.5)	25.8	(13.2)	19.5	18.9	
Hospital 2	72	18.3	(11.7)	47.3	(20.6)	28.3	21.0	
MRI-guided Brachytherapy	68	21.0	(12.1)*	31.7	(16.1)** *	8.1	12.7	
All patients	226	18.7	(11.5)	38.4	(19.4)	18.9	19.7	
Urinary incontinence								
Ultrasound-guided Brachytherapy	171	3.6	(9.8)	8.3	(17.7)	8.3	17.8	0.035
Hospital 1	90	4.1	(11.3)	10.1	(17.8)	5.9	17.5	
Hospital 2	81	3.0	(7.7)	14.2	(18.8)	10.8	17.8	
MRI-guided Brachytherapy	68	4.1	(10.3)	6.9	(16.0)*	2.9	14.2	
All patients	239	3.8	(9.9)	10.6	(17.8)	6.7	17.0	
Bowel problems								
Ultrasound-guided Brachytherapy	176	4.0	(6.9)	9.0	(10.7)	4.9	9.9	0.89
Hospital 1	92	3.6	(6.1)	7.6	(9.9)	3.9	8.8	
Hospital 2	84	4.4	(7.6)	10.6	(11.3)	6.1	10.8	
MRI-guided Brachytherapy	69	4.3	(6.0)	8.5	(9.4)	4.8	9.4	
All patients	245	4.1	(6.6)	8.9	(10.3)	4.9	9.7	
Sexual function								
Ultrasound-guided Brachytherapy	168	39.5	(39.0)	50.8	(35.5)	11.3	28.7	0.95
Hospital 1	88	46.3	(40.1)	52.3	(36.9)	7.4	23.8	
Hospital 2	80	31.5	(36.4)	49.2	(34.0)	15.5	32.8	
MRI-guided Brachytherapy	68	23.0	(31.4)** *	33.3	(33.5)** *	11.5	25.1	
All patients	236	34.8	(37.7)	45.8	(35.7)	11.4	27.6	

Table 3. Mean treatment-related function scores at baseline, at 12 months after treatment and changes for patients who completed responses.

	Patients Responding	Baseline Score	Baseline (SD)	12 Months Score	12 Months (SD)	Baseline to 12 mo. Change Score	Baseline to 12 mo. Change (SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	150	17.8	(11.1)	26.4	(14.6)	8.7	(15.2)	0.005
Hospital 1	86	17.4	(10.5)	25.8	(13.2)	8.5	(15.1)	
Hospital 2	68	18.3	(11.7)	27.1	(16.3)	8.9	(15.5)	
MRI-guided Brachytherapy	63	21.0	(12.1)*	23.4	(13.7)	1.8	(15.3)	
All patients	209	18.7	(11.5)	25.4	(14.4)	6.7	(15.6)	
Urinary incontinence								
Ultrasound-guided Brachytherapy	154	3.6	(9.8)	7.1	(13.7)	3.9	(15.8)	0.67
Hospital 1	82	4.1	(11.3)	7.9	(15.3)	4.4	(18.0)	
Hospital 2	68	3.0	(7.7)	5.9	(11.4)	3.2	(12.5)	
MRI-guided Brachytherapy	59	4.1	(10.3)	6.8	(12.7)	2.9	(12.3)	
All patients	217	3.8	(9.9)	6.8	(13.4)	3.6	(14.8)	
Bowel problems								
Ultrasound-guided Brachytherapy	161	4.0	(6.9)	7.2	(8.9)	3.4	(9.1)	0.65
Hospital 1	86	3.6	(6.1)	6.0	(6.9)	2.7	(7.3)	
Hospital 2	75	4.4	(7.6)	8.7	(10.6)	4.1	(10.7)	
MRI-guided Brachytherapy	63	4.3	(6.0)	7.7	(11.6)	4.0	(11.6)	
All patients	224	4.1	(6.6)	7.4	(9.7)	3.6	(9.8)	
Sexual function								
Ultrasound-guided Brachytherapy	159	39.5	(39.0)	55.0	(36.6)	15.9	(30.4)	0.29
Hospital 1	88	46.3	(40.1)	59.6	(36.2)	14.1	(28.1)	
Hospital 2	71	31.5	(36.4)	49.4	(36.5)	18.1	(33.1)	
MRI-guided Brachytherapy	62	23.0	(31.4)**	35.5	(35.4)	11.1	(26.8)	
All patients	221	34.8	(37.7)	49.5	(37.2)	14.6	(29.5)	

Table 4. Mean treatment-related function scores at baseline, at 24 months after treatment and changes for patients who completed responses.

	Patients Responding	Baseline Score	Baseline (SD)	24 Months Score	24 Months (SD)	Baseline to 24 mo. Change Score	Change (SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	131	17.8	(11.1)	24.6	(14.3)	8.7**		0.0008
Hospital 1	75	17.4	(10.5)	25.8	(13.2)	6.0		
Hospital 2	46	18.3	(11.7)	26.4	(15.7)	8.6		
MRI-guided Brachytherapy	56	21.0	(12.1)*	21.9	(11.1)	-0.8		
All patients	177	18.7	(11.5)	25.5	(14.4)	5.1		
Urinary incontinence								
Ultrasound-guided Brachytherapy	134	3.6	(9.8)	9.0	(14.7)	3.9		0.05
Hospital 1	73	4.1	(11.3)	10.0	(15.3)	6.2		
Hospital 2	61	3.0	(7.7)	7.7	(14.1)	5.1		
MRI-guided Brachytherapy	49	4.1	(10.3)	4.9	(11.6)	1.1		
All patients	183	3.8	(9.9)	7.9	(14.0)	4.4		
Bowel problems								
Ultrasound-guided Brachytherapy	144	4.0	(6.9)	6.6	(9.4)	7.5		0.98
Hospital 1	83	3.6	(6.1)	6.2	(6.9)	3.6		
Hospital 2	61	4.4	(7.6)	7.2	(10.5)	3.3		
MRI-guided Brachytherapy	49	4.3	(6.0)	7.1	(10.5)	3.5		
All patients	193	4.1	(6.6)	6.8	(9.0)	3.5		
Sexual function								
Ultrasound-guided Brachytherapy	137	39.5	(39.0)	56.2	(35.4)	19.1		0.60
Hospital 1	88	46.3	(40.1)	59.6	(36.2)	13.6		
Hospital 2	71	31.5	(36.4)	49.4	(36.5)	19.4		
MRI-guided Brachytherapy	62	23.0	(31.4)***	35.5	(35.4)***	13.3		
All patients	184	34.8	(37.7)	51.6	(36.5)	15.4		

Table 5. Mean treatment-related function scores at baseline, at 36 months after treatment and changes for patients who completed responses.

	Patients Responding	Baseline Score	(SD)	36 Months Score	(SD)	Baseline to 36 mo. Change Score	(SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	89	17.8	(11.1)	20.3	(11.5)	2.3		0.68
Hospital 1	52	17.4	(10.5)	21.0	(12.0)	3.1		
Hospital 2	37	18.3	(11.7)	19.4	(10.8)	2.1		
MRI-guided Brachytherapy	28	21.0	(12.1)*	27.2	(15.5)*	3.9		
All patients	117	18.7	(11.5)	22.0	(12.8)	2.9		
Urinary incontinence								
Ultrasound-guided Brachytherapy	88	3.6	(9.8)	8.6	(13.3)	6.2		0.97
Hospital 1	51	4.1	(11.3)	10.8	(16.8)	7.7		
Hospital 2	37	3.0	(7.7)	5.7	(12.4)	3.9		
MRI-guided Brachytherapy	33	4.1	(10.3)	11.2	(18.5)	6.1		
All patients	121	3.8	(9.9)	9.3	(16.2)	6.1		
Bowel problems								
Ultrasound-guided Brachytherapy	93	4.0	(6.9)	4.9	(5.5)	1.8		0.18
Hospital 1	54	3.6	(6.1)	4.9	(5.4)	2.2		
Hospital 2	39	4.4	(7.6)	5.0	(5.8)	1.3		
MRI-guided Brachytherapy	33	4.3	(6.0)	4.7	(5.6)	0.0		
All patients	126	4.1	(6.6)	4.9	(5.5)	1.3		
Sexual function								
Ultrasound-guided Brachytherapy	96	39.5	(39.0)	60.2	(37.1)	19.6		0.11
Hospital 1	57	46.3	(40.1)	64.0	(37.0)	20.8		
Hospital 2	39	31.5	(36.4)	54.7	(37.0)	18.1		
MRI-guided Brachytherapy	33	23.0	(31.4)**	41.6	(35.8)*	9.3		
All patients	129	34.8	(37.7)	55.6	(37.5)	16.8		

Table 6. Mean treatment-related function scores at baseline, at 48 months after treatment and changes for patients who completed responses.

	Patients Responding	Baseline Score	(SD)	48 Months Score	(SD)	Baseline to 48 mo. change Score	(SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	46	17.8	(11.1)	20.3	(11.5)	1.8		0.57
Hospital 1	25	17.4	(10.5)	21.1	(8.9)	3.1		
Hospital 2	21	18.3	(11.7)	15.3	(8.0)	-1.7		
MRI-guided Brachytherapy	13	21.0	(12.1)*	32.1	(16.5)**	4.6		
All patients	59	18.7	(11.5)	21.5	(12.3)	2.4		
Urinary incontinence								
Ultrasound-guided Brachytherapy	49	3.6	(9.8)	11.0	(18.2)	7.7		0.89
Hospital 1	26	4.1	(11.3)	15.0	(21.2)	11.5		
Hospital 2	23	3.2	(13.9)	6.5	(11.5)	3.2		
MRI-guided Brachytherapy	13	4.1	(10.3)	12.3	(19.2)	6.9		
All patients	62	3.8	(9.9)	11.3	(18.2)	7.5		
Bowel problems								
Ultrasound-guided Brachytherapy	50	4.0	(6.9)	5.3	(6.1)	2.3		0.52
Hospital 1	28	3.6	(6.1)	4.0	(5.4)	0.9		
Hospital 2	22	4.4	(7.6)	7.0	(7.4)	4.0		
MRI-guided Brachytherapy	14	4.3	(6.0)	10.7	(11.8)*	3.9		
All patients	64	4.1	(6.6)	6.5	(8.0)	2.6		
Sexual function								
Ultrasound-guided Brachytherapy	49	39.5	(39.0)	63.9	(36.9)	24.7		0.30
Hospital 1	29	46.3	(40.1)	71.4	(33.1)	25.0		
Hospital 2	20	31.5	(36.4)	53.1	(40.3)	24.4		
MRI-guided Brachytherapy	11	23.0	(31.4)**	50.0	(38.4)	12.6		
All patients	60	34.8	(37.7)	61.4	(37.3)	22.2		